



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

FEB 23 2010

The Honorable Edward J. Markey
Chairman
Subcommittee on Energy and Environment
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

Thank you for your letter of January 5, 2010, to the Food and Drug Administration (FDA or the Agency), requesting information regarding our plans to finalize our regulation of over-the-counter (OTC) topical antiseptic drug products, including soaps and hand sanitizers. Please note that FDA is in the midst of conducting rulemaking and is also considering a Citizen Petition relating to the use of triclosan in products regulated by FDA, both of which involve similar questions to some you have raised. Thus, FDA has not yet reached final conclusions on some of these matters. We have restated your 11 questions below in bold, followed by our responses.

1. What is the status of the final monograph ruling? When does FDA plan on promulgating finalized rules regarding over-the-counter topical antimicrobial products? Please provide a detailed timeline.

FDA is working to issue a proposed rule to amend the 1994 tentative final monograph (TFM) for OTC health care antiseptic drug products.¹ This will permit us to incorporate the most up-to-date data and information into the monograph and ensure that the data meet FDA standards for safety and efficacy. In developing the proposed rule, we have reviewed the available safety and effectiveness data for active ingredients under consideration in the topical antimicrobial monograph, which includes triclosan and triclocarban. As discussed below, new questions have been raised about the widespread use of antimicrobial ingredients in these products (e.g., the potential of antimicrobial products to increase antibiotic resistance and to cause endocrine disruption). The proposed rule we plan to issue will seek, among other things, additional data regarding the safety and effectiveness of topical antimicrobial products for consumer use where available data are not sufficient to resolve issues. Once published, the public will be given a specified time period to respond to the proposed rule with comments and the submission of new data. We will then use these comments and data to prepare a final rule. Although we cannot give you a detailed timeline for completion of this process, we are working diligently to publish the proposed rule and will finalize the rule as quickly as possible thereafter.

2. In your 1994 Tentative Final Monograph, you say that:

"The agency sees no reason to continue to include "antimicrobial soap" as a separate product category. Soap is considered to be a dosage form, and specific dosage forms are not being included in the monograph unless there is a particular safety or efficacy reason for doing so. Antimicrobial ingredients may be formulated as soaps for some of the uses discussed in this document, e.g., handwash; however, the designation "antimicrobial soap" is no longer being proposed for inclusion in the monograph."

¹ The 1994 TFM (59 FR 31402, June 17, 1994) can be viewed on FDA's Web site at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm070821.htm>. As reflected on the current Unified Regulatory Agenda, FDA is planning to finalize the topical antimicrobial drug products monograph in four separate segments, addressing topical antimicrobial drug products intended for use by consumers, by health care workers, and by food handlers separately. (http://fwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2009_unified_agenda&docid=f_ua091206.wais). This will permit FDA to separately assess each of these uses, and analyze the unique risk-benefit profile for each use.

What products are covered by the monograph? Please provide a detailed list. How would the agency treat a handsoap or bodywash that makes an antibacterial claim? If these products are not subject to the monograph, please provide a rationale, in light of the evidence that these agents may be both ineffective and unsafe. Has the FDA concluded that there is no particular safety or efficacy reason for treating these products separately?

The TFM covers antibacterial active ingredients for consumer and health care professional use in a number of different formulations. The four product categories covered are (1) consumer antibacterial soaps and washes, (2) health care personnel handwashes, (3) patient preoperative skin preparations, and (4) surgical hand scrubs. A list of the active ingredients covered by the monograph is enclosed.

Antibacterial soaps and washes continue to be subject to regulation under the topical antimicrobial drug products monograph. The changes you refer to above were intended to make the structure of the monograph more consistent with that of other monographs by not having separate product categories based only on dosage form differences. None of these changes alter the fact that soaps for use on the skin that bear antimicrobial claims, including those for personal or home use, remain subject to the OTC monograph.

3. Has the FDA reviewed the scientific evidence regarding the endocrine disrupting nature of triclosan and triclocarban? If yes, what has the FDA concluded? If not, why not?

FDA shares your concern over the potential effects of triclosan and triclocarban as endocrine disruptors that have emerged since we issued the TFM in 1994. It has been reported, for example, that triclosan decreases thyroxine levels in a rat model² and decreases the levels of androgens, leading to decreased sperm production in treated male rats, which indicates a potential perturbation in the hypo-pituitary-gonadal axis.³ Triclocarban, in turn, has been reported to enhance testosterone action in experimental studies, both *in vitro* and *in vivo* (in male rats).⁴ Finally, there are some *in vitro* studies, as well as studies in several different animal species (including mammals), that suggest triclosan may interfere with the thyroid system and have other endocrine-disrupting effects, possibly through the inhibition of sulfonating and glucuronating enzymes.⁵ It is FDA's opinion that existing data raise valid concerns about the effects of repetitive daily human exposure to these antiseptic ingredients.

FDA will continue to review all newly available scientific literature on the endocrine disruption activity of triclosan and triclocarban. We are also working with the Environmental Protection Agency (EPA) to coordinate assessment of the potential for endocrine disruption for all ingredients that fall within the jurisdictions of both agencies under EPA's Endocrine Disruptor Screening Program (EDSP). The cumulative result of our work is providing a framework for implementing changes to the TFM discussed above.

² Paul, et al. (2010). "Short-Term Exposure to Triclosan Decreases Thyroxine In Vivo Via Upregulation of Hepatic Catabolism in Young Long-Evans Rats." Toxicological Sciences, 113(2):367-79, 2010.

³ Kumar, et al. (2009). "Alteration of Testicular Steriodogenesis and Histopathology of Reproductive System in Male Rats Treated with Triclosan." Reproductive Toxicology, 27:177-85, 2009.

⁴ Chen, et al (2008). "Triclocarban Enhances Testosterone Action: A New Type of Endocrine Disruptor?" Endocrinology, 149(3): 1173-91179, 2008; and Zorrilla, I.M., et al., "The Effects of Triclosan on Puberty and Thyroid Hormones in Male Wistar Rats," Toxicological Sciences, 107:56-64, 2009.

⁵ Ahn, K.C., et al., "In Vitro Biologic Activities of the Antimicrobials Triclocarban, Its Analogs, and Triclosan in Bioassay Screens: Receptor-Based Bioassay Screens," Environmental Health Perspectives, 116: 1203-1210, 2008; Crofton, K.M, et al., "Short-Term In Vivo Exposure to the Water Contaminant Triclosan: Evidence for Disruption of Thyroxine," Environmental Toxicology and Pharmacology, 24:194-197, 2007; Zorrilla, I.M. at 56-54; James, M.O. et al., "Triclosan Is a Potent Inhibitor of Estradiol and Estrone Sulfonation in Sheep Placenta," Environmental International, 2009; Chen, J. et al., "Triclocarban Enhances Testosterone Action: A New Type of Endocrine Disruptor?" Endocrinology, 149: 1173-9, 2008; Allmyr, M., et al., "Human Exposure to Triclosan Via Toothpaste Does Not Change CYP3A4 Activity or Plasma Concentrations of Thyroid Hormones," Basic and Clinical Pharmacology and Toxicology, 2009; Gee, R.H., et al., "Oestrogenic and Androgenic Activity of Triclosan in Breast Cancer Cells," Journal of Applied Toxicology, 28: 78-91, 2008; Jacobs, M. N., et al., "Lignans, Bacteriocides and Organochlorine Compounds Activate the Human Pregnane X Receptor (PXR)," Toxicology and Applied Pharmacology, 209:123-133, 2005; Kumar, V. C., et al., "Disruption of LH-Induced Testosterone Biosynthesis in Testicular Leydig Cells by Triclosan: Probable Mechanism of Action," Toxicology, 250:124-131, 2008; and Kumar, V., et al., "Alteration of Testicular Steroidogenesis and Histopathology of Reproductive System in Male Rats Treated with Triclosan," Reproductive Toxicology, 27:177-185, 2009.

4. Has the FDA itself assessed the low dose, long term health and environmental impacts of these compounds? If yes, what, if anything, has the FDA concluded? If not, does FDA plan to do so?

FDA shares your concerns about the potential long-term impact of these chemicals on human health and the environment. As discussed below, we are working to quantify these impacts. Because triclosan and triclocarban are used in a wide variety of products from pesticides and cleaning agents to hand soaps, toothpaste and cotton swabs, it is challenging to conduct meaningful studies that can accurately characterize exposure to these chemicals in all settings where exposure occurs. We have partnered with EPA to assess the impact of these products on human health through assessment of existing health and environmental data. We are working to identify any specific areas where data are insufficient, incomplete, or where scientific information is totally lacking. FDA is using this information as a basis for revising the TFM.

Human Health Effects of Triclosan:

There are several reasons for our examination of triclosan's safety and potential impact on human health, including the following:

- A significant portion of the U.S. population, both children and adults, have had sustained use of, or exposure to, triclosan.
- There are little long-term data on the effects of dermal application, a known method of triclosan exposure.
- There is a lack of sufficient studies and/or data on the reproductive/developmental toxicity and endocrine disruption potential for triclosan.

In 1994, FDA concluded that triclosan should be classified as a Category III ingredient (59 FR 31402, June 17, 1994), meaning that the Agency could not determine whether this ingredient was safe and effective because of insufficient data. In 1997, FDA approved a New Drug Application (NDA) for Colgate Total Toothpaste, a product containing 0.3% triclosan. The NDA sponsor conducted a toxicological assessment before the drug's approval, which included an oral carcinogenicity study. After review of this study, FDA concluded that triclosan used in a toothpaste was not likely to be carcinogenic in humans following long-term oral exposure.⁶ Based upon this finding and upon studies demonstrating a clinical benefit from the use of Colgate Total, FDA approved the NDA.

Since that time, questions have arisen regarding the health effects of triclosan. During this period, FDA has been involved in ongoing scientific investigations of the chemical. We have reviewed EPA's Reregistration Eligibility Decision (RED) for triclosan. Although the RED is focused on EPA's conclusions of the potential risks to human health and the environment resulting from uses of triclosan as a registered pesticide, it includes an analysis of all available data on triclosan's endocrine effects, developmental and reproductive toxicity, chronic toxicity, and carcinogenicity. The RED relied, in part, on 2003-04 data from the National Health and Nutrition Examination Survey (NHANES) measurements of urinary concentrations of triclosan in the U.S. population, which would include all triclosan-related exposure. Urinary monitoring results from 2005-06 have been recently released. We will review this data and, through the revision of the TFM, detail our concerns and seek to obtain additional data on the potential for long-term negative impacts from exposure to this chemical.

To aid in the collection of additional data on long-term dermal exposure, FDA has also nominated triclosan to the National Toxicology Program (NTP) through the Agency's National Center for Toxicological Research (NCTR). The NTP work on triclosan has begun and includes a dermal carcinogenicity study along with a series of reproductive/developmental toxicity studies designed to provide data on the effects of long-term triclosan exposure. As with our endocrine-disruption review, FDA plans to seek data through our future rulemakings on antimicrobial products to address any data gaps that we identify during this work.

Human Health Effects of Triclocarban:

⁶ At the time of the 1997 approval of the NDA Colgate Total Toothpaste, the scientific community had not raised concerns pertaining to endocrine disruption associated with triclosan. Accordingly, we did not seek endocrine-disruption data in conjunction with this NDA.

FDA has dealt with triclocarban on a more limited basis than triclosan. We do not have sufficient data to draw conclusions about potential long-term health effects of triclocarban and therefore plan to identify concerns in the current monograph rulemaking process to obtain any data that may assist us in drawing solid conclusions about its potential health effects.

Environmental Exposure:

We have reviewed much of the literature available on long-term, low-dose effects of triclosan exposure on the environment, including the effects of triclosan on aquatic organisms. (b) (4)

Our collaboration with EPA also provides a critical avenue for obtaining much-needed comprehensive data. FDA has reviewed the environmental assessments on triclosan associated with EPA's RED referenced above. From our preliminary review, the available data suggest that green algae is the most sensitive species to triclosan, and is negatively affected at low levels ($EC_{50}=0.0012 \text{ mg/L}$).^{7,8,9,10,11} In addition, triclosan exposure has reportedly given rise to toxicity in other aquatic organisms, such as fish and invertebrates.¹² EPA requires pesticide registrants to include labeling on triclosan-containing products indicating the chemical's toxicity to fish and other aquatic life, and mandates that discharges to waterways must be in compliance with a National Pollutant Discharge Elimination System (NPDES) permit. FDA will continue to seek data on environmental exposure through EAs submitted as part of the drug application process, and to work with EPA to quantify the data received and to respond appropriately to the analytical findings.

5. Would FDA proceed differently with its rule-making for these products if it determines that the route of human exposure to triclosan or triclocarban is through ingestion of contaminated drinking water and not through dermal absorption during the course of its intended use? Please explain.

FDA has generally focused on human health effects of triclosan from direct, intentional use because we believe this is a more significant mechanism of human exposure. Although it is not within FDA's purview to assess or set drinking water standards for water contaminants, we are working with the EPA to perform these assessments and address the sources of triclosan in the environment. Measurements of triclosan in finished drinking water are generally very low (with a maximum detection level of only 43 nanograms/liter).^{13,14} As we understand it, EPA's current view (as evidenced by the third contaminant candidate list (October 8, 2009)) is that triclosan and triclocarban residues do not occur in water at levels approaching levels of health concern.

⁷ Chalew TEA.E.A., Halden RU. 2009. R.U. "Environmental Exposure of Aquatic and Terrestrial Biota to Triclosan and Triclocarban," Journal of the American Water Resources Association, 45:4-13, 2009.

⁸ Coogan MA, M.A., Edziyie RE, R.E., La Point TW, T.W., Venables BJ. 2007. B.J. "Algal Bioaccumulation Of Triclocarban, Triclosan, and Methyl-Triclosan in a North Texas Wastewater, Treatment Plant Receiving Stream." Chemosphere, 67:1911-1918, 2007.

⁹ Dynes JJ, J.J., Lawrence JR, J.R., Korber DR, D.R., Swerhone GDW, G.D.W., Leppard GG, G.G., Hitchcock AP. 2009. , A.P. "Morphological and Biochemical Changes in *Pseudomonas Fluorescens* Biofilms Induced by Sub-Inhibitory Exposure to Antimicrobial Agents," Canadian Journal of Microbiology, 55:163-178., 2009.

¹⁰ Orvos DR, D.R., Versteeg DJ, D.J., Inauen, J., Capdevielle, M., Rothenstein, A., Cunningham, V. 2002. "Aquatic Toxicity of Triclosan," Environmental Toxicology and Chemistry, 21:1338-1349., 2002.

¹¹ United States Environmental Protection Agency. 5-Chloro-2-(2,4-dichlorophenoxy)phenol (Triclosan): Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Case No 2340. DP Barcode 343544. PC Code: 054901.

¹² Chalew at 4-13.

¹³ Stackelberg PE, P.E., Furlong ET, E.T., Meyer MT, M.T., Zaugg SD, S.D., Henderson AK, A.K., Reissman DB. 2004. , D.B. "Persistence of Pharmaceutical Compounds and Other Organic Wastewater Contaminants in a Conventional Drinking-Water Treatment Plant," Science of the Total Environment, 329:99-113, 2004.

¹⁴ Snyder, et al. 2008. "Removal of EDCs and Pharmaceuticals in Drinking and Reuse Treatment Processes." Water Intelligence Online, 372, 2008.

6. In 2008, the Environmental Protection Agency (EPA) Re-registration eligibility decision (RED) document required label changes to reflect the environmental hazards posed by end-use products such as pesticides that contain triclosan. This labeling requirement states:

“Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit and the permitting authorities are notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of EPA.”

Given the fact that triclosan used in products under FDA’s jurisdiction are consistently washed down the drain and into sewage treatment systems, do you think that personal products should be similarly labeled? Why or why not?

The triclosan RED, issued by EPA’s Office of Pesticide Programs, indicates that the labeling requirement is intended for “manufacturing-use” products and not for “end-use” products.¹⁵ In addition, EPA states that placing these statements on large, end-use containers and on all technical grade and manufacturing-use containers will provide an adequate reminder to the applicable pesticide producers and users of their obligations with respect to effluent discharges.¹⁶ In FDA’s view, the label statement contains technical information intended solely for industrial manufacturers and is not applicable to end-use products, such as antimicrobial soaps and handwashes, for use by individual consumers. Because the label statement includes language such as “discharge of effluent” and “NPDES Permit,” we believe the statement would not be understood by ordinary consumers and would likely create consumer confusion if included on handwash products. Accordingly, in FDA’s view, this label statement would not be appropriate for FDA-regulated, personal “end-use” products, such as antimicrobial hand and body soaps.

7. The National Environmental Policy Act (NEPA) requires all federal agencies, including the FDA, to assess the environmental impacts of any proposed actions. Has the FDA performed an environmental assessment, or prepared a detailed statement of environmental impact, on the use and disposal of these antimicrobial agents, as it has for other products such as prescription drugs? If so, please provide a copy, and if not, why not?

Where required by NEPA regulations, FDA obtains EAs in conjunction with the submission of drug applications.

(b) (4)

In addition, FDA has just published a request for data and information regarding the potential environmental impact of certain OTC monograph ingredients, including triclosan.¹⁷ Any data and information received will be included in FDA’s analysis of triclosan’s effect on the environment.

8. Has the FDA evaluated the efficacy of antiseptic washes used by consumers in reducing transmission of infection? Has the FDA determined that use of antiseptic handwashes is superior to washing hands with regular soap using proper handwashing technique? If so, please describe the manner in which this demonstration was made.

FDA evaluated all the available data for evidence of a clinical benefit from the use of consumer antibacterial washes. Analysis of many of these studies was presented to the Nonprescription Drugs Advisory Committee at a

¹⁵ See RED, Table 10, at <http://www.epa.gov/oppsrrd1/REDs/2340red.pdf>.

¹⁶ The above Labeling Statement is detailed in EPA PR Notice 93-10 (http://www.epa.gov/PR_Notices/pr93-10.pdf), published on July 29, 1993. On May 1, 1995, PR Notice 95-1 (http://www.epa.gov/PR_Notices/pr95-1.html) revised the scope of PR Notice 93-10 to exempt *end-use products in containers of less than 5 gallons (liquid), less than 50 pounds (solid, dry weight) and in aerosol containers of any size*. See EPA Label Review Manual Chapter 8: Environmental Hazards/VII. Miscellaneous Statements (<http://www.epa.gov/oppfead1/labeling/lrm/chap-08.htm>).

EPA provides definitions for Manufacturing-Use Product and End-Use Product at http://www.epa.gov/oppfead1/guidance/product-sop.htm#_1_5.

¹⁷ “Safety and Efficacy Review for Additional Ingredients in Over-the-Counter Drug Products for Human Use; Request for Environmental Impact Data and Information” (75 FR 7606, February 22, 2010).

meeting on the risks and benefits of antiseptics for consumer use in October 2005. At that time, FDA was not aware of any evidence that antibacterial washes were superior to plain soap and water for reducing transmission of or preventing infection for consumers. The FDA analysis, along with the recommendations of the Advisory Committee, is being considered as a part of the current process of amending the monograph.

9. What percentage of consumer “antibacterial” soaps, including liquid and bar soaps contain triclosan or triclocarban?

FDA believes that the majority of consumer antibacterial soaps contain triclosan or triclocarban as active ingredients. A 2001 physician-performed survey of the prevalence of consumer antibacterial soaps on the market found that, of national brand soaps (plain and antibacterial) available at national chains, regional grocery and Internet stores, triclosan or triclocarban was found in 76 percent of 395 liquid and 29 percent of 733 bar soaps.¹⁸

10. To what extent has the FDA evaluated the claim that some antimicrobial products may increase antibiotic resistance? Has the FDA completed or does it plan to complete a thorough survey of the published literature to determine whether antibiotic resistance has been reported for triclosan and triclocarban? Does FDA plan to consider this potential impact in its consideration of whether these products are safe and effective? Why or why not?

FDA is concerned about the role that antibacterial products may play in the development of antibiotic resistance and has sought the advice from expert panels on this topic on two occasions. In 1997, a joint Nonprescription Drugs and Anti-Infective Drugs Advisory Committee concluded that the data were not sufficient to take any action on this issue at that time. However, the joint Committee recommended that FDA work with industry to establish surveillance mechanisms to address antiseptic and antibiotic resistance. At an October 2005 Nonprescription Drugs Advisory Committee (NDAC) meeting on antiseptics for consumer use, some NDAC members expressed concern about the societal consequences of the pervasive use of consumer antibacterial products, including the ecotoxic potential of certain antibacterial active ingredients. FDA’s evaluation of the data, along with the NDAC recommendations, has been considered in our current proposal to amend the 1994 TFM. FDA has continued to evaluate this issue and has evaluated all of the available data concerning the possibility that antiseptic use may contribute to the development of antibiotic resistance.

FDA has also worked to review the available literature correlating reduced susceptibility to antibacterial active ingredients and antibiotic resistance (cross-resistance) and exposure to either triclosan or triclocarban. The review encompasses all of the active ingredients commonly used in consumer products, which includes triclosan; however, FDA did not find any data on triclocarban. There are numerous laboratory studies that evaluated cross-resistance between antiseptics and antibiotics.¹⁹ These studies suggest that it is relatively easy for bacteria to develop altered

¹⁸ Perencevich, E.N., Wong, M.T., and Harris, A.D. “National and Regional Assessment of the Antibacterial Soap Market: A Step Toward Determining the Impact of Prevalent Antibacterial Soaps,” American Journal of Infection Control, 29:281-283, 2001.

¹⁹ Braoudaki, M., and Hilton, A.C. “Adaptive Resistance to Biocides in *Salmonella enterica* and *Escherichia coli* O157 and Cross-Resistance to Antimicrobial Agents,” Journal of Clinical Microbiology, 42:73-78, 2004; Brenwald, N.P., and Fraiese, A.P. “Triclosan Resistance in Methicillin-Resistant *Staphylococcus aureus* (MRSA),” Journal of Hospital Infection, 55:141-144, 2003; Chuanchuen, R., et al., “Cross-Resistance between Triclosan and Antibiotics in *Pseudomonas aeruginosa* Is Mediated by Multidrug Efflux Pumps: Exposure of a Susceptible Mutant Strain to Triclosan Selects *rfxB* Mutants Overexpressing MexCD-OprJ,” Antimicrobial Agents and Chemotherapy, 45:428-432, 2001; Cookson, B.D., et al., “Transferable Resistance to Triclosan in MRSA,” Lancet, 337:1548-1549, 1991; Karatzas, K.A., et al., “Prolonged Treatment of *Salmonella enterica* serovar Typhimurium with Commercial Disinfectants Selects for Multiple Antibiotic Resistance, Increased Efflux and Reduced Invasiveness,” Journal of Antimicrobial Chemotherapy, 60:947-955, 2007; Randall, L.P., et al., “Effect of Triclosan or a Phenolic Farm Disinfectant on the Selection of Antibiotic-Resistant *Salmonella enterica*,” Journal of Antimicrobial Chemotherapy, 54:621-627, 2004; Sanchez, P., Moreno, E., and Martinez, J.L. “The Biocide Triclosan Selects *Stenotrophomonas maltophilia* Mutants That Overproduce the SmeDEF Multidrug Efflux Pump,” Antimicrobial Agents and Chemotherapy, 49:781-782, 2005; Ledder, R.G., et al., “Effects of Chronic Triclosan Exposure Upon the Antimicrobial Susceptibility of 40 Ex-situ Environmental and Human Isolates,” Journal of Applied Microbiology, 100:1132-1140, 2006; Braoudaki, M., and Hilton, A.C. “Low Level of Cross-Resistance Between Triclosan and Antibiotics in *Escherichia coli* K-12 and *E. coli* O55 Compared to *E. coli* O157,” FEMS Microbiology Letters,

susceptibilities to both antiseptics and antibiotics in the laboratory setting. However, overall, there was no definitive correlation between altered susceptibility to antibacterial active ingredients and antibiotics. Although the clinical relevance of these laboratory studies is not clear, FDA continues to believe that the possibility that antiseptics contribute to changes in antibiotic susceptibility warrants further evaluation. The proposed rule FDA plans to issue will request additional data where available data are not sufficient to resolve issues.

11. Will the FDA's proposed rulemaking regulate chemicals used in consumer handwashes differently than those marketed for and used by health care professionals? Please explain.

The monograph system is sufficiently flexible to permit FDA to differentiate between the treatment of consumer and health care professional products. FDA is planning on regulating these products in separate segments of the antimicrobial drug products monograph. In the 1994 TFM, FDA did not propose to distinguish between consumer handwash products and those products marketed for use by health care professionals.²⁰ Since that time, we have concluded that these use settings differ in important ways. For instance, in the hospital setting, the risk of exposure to pathogenic bacteria is high within a population that includes many individuals with weakened immune systems and an increased risk for serious infections. In the consumer setting, by contrast, the target population is composed of generally healthy individuals and the risk of infection is relatively low. Because the risks and benefits are generally very different between these populations, FDA believes that it may be appropriate for the monograph to make a distinction between the category of products for consumers and those intended for use by health care professionals.

Thank you for your interest in this matter. Information contained in this letter may include information that is trade secret, commercial confidential, or other information protected from disclosure to the public under the Freedom of Information Act (Title 5, *United States Code* [U.S.C.] 552), the Trade Secrets Act (18 U.S.C. 1905), the Privacy Act (5 U.S.C. 552a), and FDA regulations. The Committee should not publish or otherwise make public any such information. We would be glad to discuss with the Committee staff the protected status of any specific information. If we can be of further assistance, please let us know.

Sincerely,



Jeanne Ireland
Assistant Commissioner
for Legislation

Enclosure

cc: -The Honorable Henry A. Waxman
Chairman
-The Honorable Joe Barton
Ranking Member
-The Honorable Fred Upton
Ranking Member
Subcommittee on Energy and Environment

235:305-309, 2004; Randall, L.P., et al., "Prevalence of Multiple Antibiotic Resistance in 443 *Campylobacter* spp. Isolated from Humans and Animals," *Journal of Antimicrobial Chemotherapy*, 52:507-510, 2003; Seaman, P.F., Ochs, D., and Day, M.J., "Small-Colony Variants: A Novel Mechanism for Triclosan Resistance in Methicillin-Resistant *Staphylococcus aureus*," *Journal of Antimicrobial Chemotherapy*, 59:43-50, 2007; Chen, Y., et al., "Triclosan Resistance in Clinical Isolates of *Acinetobacter baumannii*," *Journal of Medical Microbiology*, 58:1086-1091, 2009; Bırosova, L. and Mikulasova, M., "Development of Triclosan and Antibiotic Resistance in *Salmonella enterica* serovar Typhimurium," *Journal of Medical Microbiology*, 58:436-441, 2009.

²⁰ 59 Federal Register 31402, See FDA's notice of proposed rulemaking, "Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-care Antiseptic Drug Products," (59 FR 31402, June 17, 1994).

Active Ingredients Covered by the Tentative Final Monograph for Topical Antiseptics

1. Alcohol, 60 to 95 percent
2. Benzalkonium chloride
3. Benzethonium chloride
4. Chloroxylonol
5. Cloflucarban*
6. Fluorosalan*
7. Hexachlorophene*
8. Hexylresorcinol
9. Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
10. Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
11. Iodine topical solution USP
12. Isopropyl alcohol, 70 to 91.3 percent
13. Mercufenol chloride
14. Methylbenzethonium chloride
15. Nonylphenoxypoly (ethyleneoxy) ethanoliiodine
16. Phenol (less than 1.5 percent)
17. Phenol (greater than 1.5 percent)*
18. Poloxamer-iodine complex
19. Povidone-iodine, 5 to 10 percent
20. Secondary amyltricresols
21. Sodium oxychlorosene
22. Tribromsalan*
23. Triclocarban
24. Triclosan
25. Undecylium chloride iodine complex

*Not Generally Recognized as Safe and Effective for some or all antiseptic uses, but evaluated under the OTC Drug Review